IN THE CLAIMS

Applicant hereby cancels claims 1-21 without prejudice to further prosecution at a later date.

Conclusion

Examination and allowance of claims 22-35 is requested.

Respectfully Submitted,

Date: September 29, 2003

Stephen Donovan
Registration Number 33,433

Please direct all inquiries and correspondence to:

Stephen Donovan
Allergan, Inc.
2525 Dupont Drive, T2-7H
Irvine, California 92612

Telephone: 714 246 4026
Fax: 714 246 4249

CERTIFICATE OF EXPRESS MAILING UNDER 37 C.F.R. §1.10

I hereby certify that this Preliminary Amendment and the documents referred to as enclosed therein are being deposited with the United States Postal Service on this date September 29, 2003 in an envelope as "Express Mail Post Office to Addressee" Mailing Label number EV295682885US addressed to Mail Stop: Patent Application, Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450

Susan Bartholomew
Name of person mailing paper

Date: September 29, 2003

Signature of person signing paper

AMENDED PAGE ONE OF THE SPECIFICATION

TRANSDERMAL BOTULINUM TOXIN ADMINISTRATION~~COMPOSITIONS~~

by

Stephen Donovan

CROSS REFERENCE

This application is a divisional of pending application serial number 10/194,805, filed July 11, 2002.

The present invention relates to pharmaceutical compositions containing neurotoxins. In particular, the present invention relates to compositions containing clostridial neurotoxins, such as botulinum toxin, for transdermal topical administration to patients.

BACKGROUND

Botulinum Toxin

The genus *Clostridium* has more than one hundred and twenty seven species, grouped according to their morphology and functions. The anaerobic, gram positive bacterium *Clostridium botulinum* produces a potent polypeptide neurotoxin, botulinum toxin, which causes a neuroparalytic illness in humans and animals referred to as botulism. The spores of *Clostridium botulinum* are found in soil and can grow in improperly sterilized and sealed food containers of home based canneries, which are the cause of many of the cases of botulism. The effects of botulism typically appear 18 to 36 hours after eating the foodstuffs infected with a *Clostridium botulinum* culture or spores. The botulinum toxin can apparently pass unattenuated through the lining of the gut and attack peripheral motor neurons. Symptoms of botulinum toxin intoxication can progress from difficulty walking, swallowing, and speaking to paralysis of the respiratory muscles and death.

Botulinum toxin type A is the most lethal natural biological agent known to man. About 50 picograms of a commercially available

AMENDED CLAIMS

Claims 1-21 (cancelled).

22. (Original) A method of reducing neurotransmitter release in a subdermal structure of a patient, the method comprising the steps of:

(a) non-chemically disrupting the stratum corneum of the patient's skin to reduce impermeability of the stratum corneum; and

(b) applying botulinum toxin to the skin of the patient in an area that has had the stratum corneum disrupted in step (a).

23. (Original) The method of claim 22, wherein the stratum corneum is disrupted by abrasively removing the stratum corneum.

24. (Original) The method of claim 22, wherein the stratum corneum is disrupted by applying an adhesive material to the patient's skin, and removing the adhesive material applied thereto.

25. (Original) The method of claim 22, wherein the stratum corneum is disrupted by applying ultrasound at a frequency between 20 kHz and less than 10 MHz at an intensity that does not permanently damage the patient's skin.

26. (Original) The method of claim 22, wherein the stratum corneum is disrupted by passing electrical current from a first point on the patient's skin to a second point on the patient's skin.

27. (Original) The method of claim 26, wherein the electrical current is passed to create a plurality of pores in the stratum corneum to enhance passage of botulinum toxin to the subdermal structures.

28. (Original) The method of claim 22, wherein the botulinum toxin is selected from a group of botulinum toxins consisting of types A, B, C, D, E, F, and G.

29. (Original) The method of claim 22, wherein the botulinum toxin is applied in a pharmaceutical composition comprising an enhancing agent for enhancing the delivery of the botulinum toxin through the skin.

30. (Original) The method of claim 22, wherein the botulinum toxin is incorporated into a transfer some.

31. (Original) A method of relieving pain in a patient caused by a spastic muscle, the method comprising the steps of:
(a) applying ultrasound at a frequency between about 10 kHz and 1 MHz to the patient's skin overlying the spastic muscle; and
(b) applying botulinum toxin to the patient's skin that has received the ultrasound in step (a).

32. (Original) The method of claim 31, further comprising a step of abrasively removing portions of the stratum corneum of the patient's skin that received the ultrasound.

33. (Original) The method of claim 31, wherein the botulinum toxin is botulinum toxin type A.

34. (Original) The method of claim 31, wherein the botulinum toxin is administered in a composition comprising an enhancing agent that facilitates penetration of the botulinum toxin through the patient's skin.

35. (Original) The method of claim 31, wherein the botulinum toxin is applied in a transdermal patch applied to the patient's skin.